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The possible relationship between patent foramen ovale and decompression sickness:

A review of the literature

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THE POSSIBLE RELATIONSHIP BETWEEN PATENT FORAMEN OVALE AND DECOMPRESSION SICKNESS: A REVIEW OF THE LITERATURE

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EXECUTIVE SUMMARY

A patent foramen ovale (PFO) is a small opening between the right and left cardiac atria, a persisting remnant of a physiologic communication present in the fetal heart. This normally closes after birth, but remains patent through to adulthood in up to a third of normal adults. A patent PFO is a potential conduit for blood clot (resulting in a stroke), or venous gas bubbles during decompression, (resulting in type II neurologic decompression sickness). There has been considerable controversy about the significance of a PFO as a possible mechanism for type II decompression sickness. Despite the high prevalence of PFO in the general population, and the relatively common occurrence of venous gas bubbles in diving and altitude exposures, the incidence of type II DCS in diving or with altitude exposure is low.

This paper reviews the literature with respect to the potential for right-to-left embolization through a PFO, relation of PFO to DCS, screening techniques for PFO, and treatment options. The literature supports a relationship between the presence and size of PFO and cryptogenic stroke (stroke, generally in younger individuals with no other identifiable risk factors). The weight of evidence also favours an increased relative risk of type II DCS with a PFO, although the absolute increase in risk accrued is small. The gold standard for PFO screening is a trans-esophageal echocardiographic (TEE) and colour flow study, but trans-cranial Doppler (TCD) with contrast is a promising technique with good accuracy compared with TEE.

ABSTRACT

There continues to be a controversy about the possible significance of patent foramen ovale (PFO) in the pathophysiology of type II decompression sickness (DCS with neurologic symptoms). PFO's are a common finding in normal persons, being present in up to a third of the population. The potential for right-to-left shunting of venous gas emboli (VGE) which are known to occur in even no-decompression dives is a theoretical concern, yet the incidence of type II DCS is remarkably low given the prevalence of PFO. Altitude decompression is analagous to decompression from a saturation dive, and VGE are observed above 15,000 feet (4572m). The potential for PFO shunting of VGE is a particular concern for space extra-vehicular activity (EVA) where the pressure in the US EVA suit is 4.3 PSI, equivalent to 30,000 feet. This paper reviews the literature with respect to the potential for right-to-left embolization through a PFO, relation of PFO to DCS, screening techniques for PFO, and treatment options. The literature supports a relationship between the presence and size of PFO and cryptogenic stroke (stroke, generally in younger individuals with no other identifiable risk factors). The weight of evidence also favours an increased relative risk of type II DCS with a PFO, although the absolute increase in risk accrued is small. The gold standard for PFO screening is a trans-esophageal echocardiographic (TEE) and colour flow study, but trans-cranial Doppler (TCD) with contrast is a promising technique with good accuracy compared with TEE.

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Embryology

The foramen ovale develops as part of the process of atrial septation. Initially in this process, a sagittal fold in the roof of the atrium develops into the septum primum, essentially separating the 2 atria. Interconnection between the atria persists via the foramen primum until the septum fuses with the atrio-ventricular (AV) endocardial cushions. In order to maintain interatrial right to left blood flow with a fused septum and closed foramen primum, a second foramen, the foramen secundum, forms just prior to septal fusion. Subsequently, a second septum, the septum secundum develops to the right of the septum primum. Like the septum primum, the septum secundum is also an incomplete barrier between the atria; the septum secundum's opening being called the fossa ovalis.

Figure 1: The Patent Foramen Ovale
(From O'Rahilly & Muller, 1992).

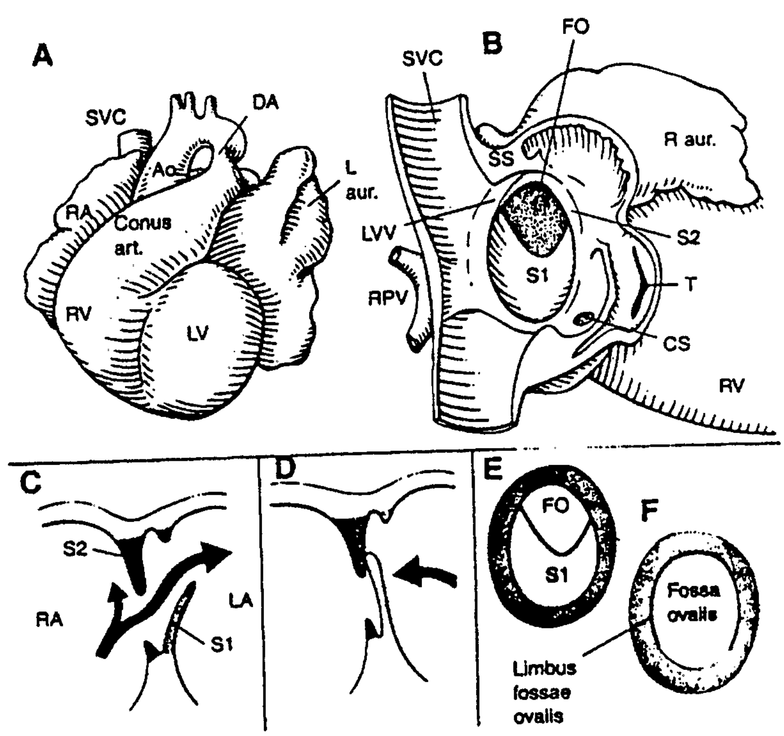

FIG. 12-11 A. Front view of the heart at 8 weeks[49]. The arch of the aorta has been pulled cranially to show the ductus arteriosus (DA) more clearly. B. Right lateral view after the right atrium has been opened. C. and D. Sections through the atria to show the valvar action of septum primum, which could close the foramen ovale if it were pressed against septum secundum. E. Right lateral view of the interatrial septum at 8 weeks, and (F) in the adult. Conus art., conus arteriosus; CS, coronary sinus; L.aur., left auricle; LVV, left venous valve; R.aur., right auricle; RPV, right pulmonary vein; SS, septum spurium; T, tricuspid valve. A and B are based on Licata.

Essentially what has taken place is somewhat analogous to drawing a Venn diagram, with the development of two apposed incomplete septa with partially overlapping fossae. The foramen ovale represents the opening that remains patent between the septae, with the septum primum acting as a valve allowing only R -> L passage of blood.

Post-natally, circulatory changes including the transfer of gas exchange from the placenta to the lungs, with resultant decrease in pulmonary vascular resistance and increased pulmonary blood flow lead to increased L atrial pressure that presses the interseptal valve against the septum secundum. Usually within the first 2 years of life the septae permanently fuse due to the development of fibrous adhesions. (O'Rahilly & Muller, 1992).

Prevalence of PFO

In some however, the foramen ovale fails to fuse. In 1984, Hagen, Scholz, & Edwards studied the prevalence of patent foramina in 965 normal hearts. Their autopsy study revealed an overall prevalence of 27.3% (see Table 1). Some have suggested that when functional imaging such as trans-esophageal echocardiography (TEE) is used in the live patient, the prevalence of patent foramen ovale (PFO) is decreased (Moon et al, 1989). In fact, in Hagen's study the prevalence of PFO was found to decline with increasing age (34.3% in first 3 decades to 25.4% in the 4th to 8th decades), so sample age distribution could lead to varying estimates of prevalence among studies. Hagen et al cite several articles in which high prevalence rates of approximately 31% were found among older patients. They attribute this lack of age-related decline to the fact that many previous studies were based on results from abnormal hearts; the implication being that altered hemodynamics of heart disease among older patients may hinder late PFO closure. Finally, among hearts with patent foramina, Hagen et al found the average foramen size to be 4.9 mm, with size increasing as age increased.

Table 1. Incidence of Patent Foramen Ovale (PFO) in Various Studies
(From Hagen et al, 1984)

Year	Authors	Number of Hearts	Incidence of PFO (%)	Age (yr) of Patients
1897	Parsons and Keith [24]	399	26	All ages
1900	Fawcett and Blachford [25]	306	31.7	>10
1918	Scammon and Norris [26]	1,809*	29	>1
1931	Patten [1]	4,083*	24.6	Mostly adults
1934	Seib [2]	500	17	20
1948	Wright et al [28]	492	22.9	Mostly adults
1972	Schroeckenstein et al [4]	144	35.4	>20
1979	Sweeney and Rosenquist [29]	64	31	>10
1984	Hagen et al	965	27.3	>1

* Combined review of literature

Clinical Detection of PFO

a. ECHOCARDIOGRAPHY

The most definitive studies on the prevalence of PFO have been autopsy studies. To determine the clinical relevance of PFO, one must have a detection method that is useful in living subjects. Transesophageal echocardiography (TEE) has been considered the gold standard in this regard, although many other detection methods have been assessed. Indeed, many studies support the view that the most accurate method for detecting PFO is TEE, but some disagree that it is the most practical.

In their study of 150 consecutive patients, Siostrzonek et al (1991) compared the detection rates of PFO in bubble contrast trans-thoracic echocardiography (TTE) and TEE (see Table 2). Detection was significantly better with contrast TEE imaging than with TTE (30/150 vs 9/150, p<.0001). There were no false positives with TTE imaging, however there were 15 (50%) false negatives and 6 (20%) undetermined cases. All of the patients with a positive TTE study also had a positive TEE, thus an unequivocal contrast TTE study negates the need for further TEE imaging. If however, the TTE is negative these authors recommend TEE in all such patients to assess for presence of PFO.

Table 2: Incidence of Positive, Negative and Undetermined Contrast Studies with Transthoracic and Transesophageal Contrast Echocardiography in 150 Patients
(From Siostrzonek et al, 1991)

	Transthoracic Contrast Echocardiography			Transesophageal Contrast Echocardiography	
	Normal Respiration	Valsalva Maneuver		Normal Respiration	Valsalva Maneuver
+	7 (5%)	9 (6%)		18 (12%)	30 (20%)
0	125 (83%)	119 (79%)		132 (88%)	120 (80%)
Undetermined	18 (12%)	22 (15%)		0 (0%)	0 (0%)

+ = positive; 0 = negative

Fischer et al (1995) assessed the prevalence of PFO in live patients. After summarizing the results of 16 studies with over 100 patients, they concluded that with TTE the prevalence of PFO was 9.3%, and with TEE was 11.2%. They went on to retro-spectively examine 1000 of their own patients with colour Doppler and contrast TEE for the presence of PFO. The prevalence of PFO was found to be 9.2%, with all 92/1000 cases detected by TEE and only 22/1000 detected by colour flow. In addition, they found that atrial septal aneurysms (ASA) were more frequent among those with PFOs, with ASA present in 15.2% with PFO compared to 6.1% of patients without PFO (p=.001). Like Hagen et al (1984), Fischer et al found an age-related decline in the prevalence of PFO.

Belkin et al (1994) compared contrast TEE with colour flow TEE, contrast TTE and colour flow TTE in 43 patients. Results of their study are summarized below in Table 3, and indicate that PFO is more frequently detected with TEE methods, and that slightly more PFOs were detected with colour Doppler than with contrast TEE.

Table 3: Data summarized from Belkin et al, 1994.

Parameter	contrast TEE	colour TEE	contrast TTE	colour TTE
nPFO (%)	14 (37%)	17 (45%)	9 (24%)	1 (3%)
Sens	gold	79%	50%	7%
Spec	gold	75%	92%	100%

Schneider et al (1996) correlated TEE directly with subsequent autopsy findings in 35 patients in order to assess the diagnostic accuracy of both colour Doppler and contrast TEE. A PFO was found in 9/35 patients at autopsy, all of which were correctly diagnosed by colour Doppler TEE, with 8/9 diagnosed correctly by contrast TEE. Others have suggested that contrast TEE is superior to both colour flow TEE and TTE in general (Moon, 1989; Hausmann, 1992; Luotolahti et al, 1995).

To further delineate TEE, Chezbraun et al (1993) compared the vertical to horizontal plane of biplane TEE in 19 contrast-positive PFO patients. They found that in the vertical plane 53% (10/19) of PFOs could be seen and sized, but none of these were visible in the horizontal plane. Although biplane echocardiography is clearly not the method of choice for PFO detection, it can be useful for determining the size and morphology of the PFO, which may be relevant for therapeutic decision making.

Although TEE provides better resolution than TTE, it is not without risks. These include esophageal injury, laryngospasm, aspiration, hypoxia, bronchospasm, and dysrhythmias. (Porembka, 1996). James (1990) notes that the Contrast Committee of the American Society of Echocardiography has record of 28 transient neurological side effects occurring in 41,000 contrast echo studies. TEE is generally considered an unpleasant procedure and IV sedation is often required. In addition, many find performing a Valsalva maneuver difficult with the probe in place. Because of the low sensitivity of TTE and the relative complexity of TEE, a simpler, but acceptably sensitive method for PFO screening was introduced in1991 by Teague and Sharma, this being transcranial Doppler (TCD).

b. VALSALVA/COUGH MANOEVERS

It is common practice to assess for the presence of PFO using the Valsalva maneuver. The rationale is that this maneuver will momentarily increase right heart pressure, thereby accentuating any right to left shunt. Some however, believe that the cough test is superior to the Valsalva in identifying the presence of PFO. (Dubourg et al, 1984; Stoddard et al, 1993)

In 1994, Jauss et al simultaneously performed TEE and TCD in 50 patients (galactose microbubbles) with and without Valsalva. Compared to TEE, the sensitivity of TCD was 100% in both conditions. Specificity without Valsalva was 47%, and increased to 93% with Valsalva (see Table 4).

Table 4: Cross Table for Transesophageal Echocardiography Compared With_Transcranial Doppler Sonography With Valsalva Maneuver
(Table 2. From Jauss et al, 1994)

	TEE		
TCD	+	-	Sum
+	14	0	14
-	1	35	36
Sum	15	35	50

TCD-trancranial Doppler sonography. TEE-transesophageal echo
+ = detection of PFO; - no detection of PFO
Sensitivity = 0.93; Specificity = 1; P<.01, Fischer's exact test

c. TRANSCRANIAL DOPPLER

In their study of 111 patients, Klotzsch et al (1994) compared contrast TEE, TTE and TCD of the left MCA as methods to identify PFO (see Table 5). With TEE, 46 PFOs were found, of which 15 were missed by TTE (accuracy of TTE 44%). In comparison, the accuracy of TCD was found to be 92.8%. The sensitivity and specificity of TCD compared to TEE were 91.3% and 93.8% respectively.

Table 5: Comparison of the ability of TEE and contrast-TCD to detect a PFO in 111 patients with cerebral ischemia
(Table 1 From Klotzsch et al, 1994.)

TCD/TEE>	Permanent	Valsalva	Negative	Totals
Permanent	19	4	2	25
Valsalva	3	16	2	21
Negative	1	3	61	65
Totals	23	23	65	111

Other studies comparing TCD to TEE demonstrate sensitivities ranging from 68 to 100% and with specificities repeatedly in the order of 100% (Di Tullio et al, 1993, Kwiecinski et al, 1994). Such results led to the conclusion that TCD is the method of choice for screening for PFO because the high sensitivity could spare patients a TEE exam. Furthermore, TCD costs less, and one can easily monitor effectiveness of the Valsalva by observing decreased cerebral blood flow (Klotzsch, 1994).

Kerut et al (1997) compared the ability of TTE, TEE and TCD to detect PFOs in both control subjects and divers referred for neurological DCS (see Table 6). TEE was the most sensitive method for detecting PFOs in both controls and divers. However, only the TCD method of imaging differentiated between divers and controls. The authors suggest that the TCD method only detects clinically significant PFOs since only strongly positive TEE also had positive TCDs.

They calculated the positive and negative predictive values for detection of shunts in DCS divers for all 3 imaging modalities. The PPV and NPV for each respectively was 52% & 59% (TEE), 62% & 58% (TTE), and 65% & 64% (TCD). Unfortunately the authours do not define "clinically relevant" and in fact when "possible DCS cases" were removed from the sample, TCD no longer differentiated between DCS and control groups.

Table 6: Right to Left Shunting During the Valsalva Maneuver
(Table 1 From Kerut et al, 1997)

	Control Subjects (n = 30)	Probable + Definite DS (n = 15)	All Divers (n = 26)
Positive Studies			
TTE	5 (17%)	3 (20%)	8 (31%)
TEE	14 (47%)	9 (60%)	15 (58%)
TD	7 (23%)	7 (47%)	13 * (50%) *

* p = 0.05 versus control
DS = decompression sickness;
TD = transcranial Doppler;
TEE = transesophageal echocardiography;
TTE = transthoracic echocardiography

Other methods such as carotid duplex monitoring, dye dilution, and oximetry have been tested as a possible method for PFO detection. Karttunun et al (1998) assessed the value of dye dilution and oximetry in detecting PFOs. They found concordance between the two methods , both of which detected PFOs in 24/59 (41%) patients. Unfortunately, they did not compare these methods to TEE, the gold standard, and so sensitivity and specificity cannot be determined. Nygren & Jogestrand compared TCD of the MCA and duplex monitoring of the ICA with TEE and found sensitivities of 100% (TCD) and 58% (duplex), and specificities of 82% and 91% respectively. The conclusion of the study was that TCD but not duplex of the ICA could be used for PFO screening.

Clinical Relevance of PFO

The rationale for such extensive investigation into the best method for detecting PFO is, of course, that detection is clinically relevant. As previously mentioned, the fact that the pressure in the left atrium is greater than that in the right atrium post-natally usually leads to PFO closure. In some however, the foramen remains patent. This is generally of no significance since the higher left atrial pressure keeps the valve functionally closed.
However, in situations where the right atrial pressure becomes significantly higher than that on the left, a gradient reversal can occur, causing right-to-left shunting through the foramen.

Gradient reversal can occur when pulmonary vessels are obstructed (e.g. from overload of venous bubbles), vasoconstriction causing increased vascular resistance and subsequent decrease in cardiac output (CO) and thus left atrial pressure, release

of Valsalva, coughing, cessation of positive pressure breathing, negative pressure breathing, restricted breathing, or any other situations leading to substantial increase in venous return to the right heart. Moon et al (1989) speculate that the prevalence of shunting in divers may be underestimated by echocardiography done in the lab because immersion in water might increase a shunt as a result of increased right atrial pressure and cardiac dilation.

In some cases, right-to-left shunting has been shown to occur occasionally during quiet breathing without complication (Fraker et al, 1979; Lynch et al, 1984; Smith et al, 1990, Apr) and generally such intermittent shunting in a normal individual may cause transient decreased oxygen saturation, but little else. Of greater concern is when such right-to-left shunting causes paradoxical embolization to occur. This phenomenon has been well-studied among stroke patients, particularly among those who experience stroke despite having no risk factors, or cryptogenic stroke.

PFO and Stroke

Jones et al (1994) examined the prevalence of PFO in 220 patients with cerebral ischemia, compared to 202 controls. Prevalence was no different in the two groups (16% vs 15% respectively). When subdivided by age groups, prevalence in PFO vs control groups remained similar in each of three age categories, <50, 50-69, >70. Similarly, Fischer et al (1995) did not find a higher prevalence of PFO among those with a history of cerebro-vascular accident (CVA). Jones et al recommended subsequent longitudinal studies in which a group of known PFO patients would be followed to assess incidence of stroke. In other words, the majority of studies to date have assessed the prevalence of PFO in stroke patients, but few if any have attempted to prove an increased incidence of stroke in a known PFO group compared to non-PFO controls.

de Belder et al (1992) examined the rates of PFO in stroke patients with and without risk factors, and controls. In this study, patients with cryptogenic strokes were 10 times more likely than controls to have PFO, and those with risk-positive strokes were 5 times more likely than controls to have PFOs. However, those with cryptogenic and risk-positive strokes were equally likely to have PFOs. Although PFOs are more frequent among patients with cryptogenic than other types of stoke, they seem to also have a high frequency among stroke patients in general compared to controls. This conclusion was also put forth by Chen et al (1991), and Petty et al (1997).

Similarly, Lechat et al (1989, abstract only) found the prevalence of PFO to be higher among stroke patients (40%) than controls (10%). When subdivided by the cause of stroke i.e. known cause, known risk factor, or cryptogenic, the prevalence of PFO rose respectively from 21%, to 40%, to 54%. Based on these results, authours suggested that paradoxical emboli through PFOs causing strokes may be more frequent than is generally believed.

Di Tullio et al (1992) used multiple logistic regression to evaluate the strength of association between PFO and cryptogenic stroke after correcting for age and stroke risk factors. They found that patients with cryptogenic stroke were 7.2 times more likely to have a PFO than were those with a known cause for stroke, thus supporting PFO as a risk factor for cryptogenic stroke. Klotzsch et al, 1994 also found PFO to occur significantly more frequently among those with cryptogenic stroke than with other known causes of stroke (see Table 7).

Table 7: PFO in 111 Patients with Known and Cryptogenic etiology of Cerebral Ischemia
(Table 2 From Klotzsch, 1994)

	PFO (+)	PFO (-)	Total
Cryptogenic	31 (77.5)	9 (22.5)	40
Large vessel disease	8 (26.5)	22 (73.3)	30
Small vessel disease	6 (30%)	14 (70%)	20
Cardioembolism	5 (26.3%)	14 (73.7%)	19
Miscellaneous	-	2	2

Frequency of PFO was significantly different in known and cryptogenic cerebral ischemia, $p <$ 0.001 (chi-square test).

Homma et al (1994) studied characteristics of PFOs that could differentiate between patients with cryptogenic strokes or strokes of known cause, since PFOs are known to be present in both types of stroke. They found that those with cryptogenic strokes were more likely to have larger PFOs with more extensive shunting, hence suggesting that the clinical significance of individual foramina may be in part determined by echocardiographically identifiable characteristics.

Stone et al (1996) used contrast TEE to subdivide a group of 34 patients with known PFO into 2 groups: a large shunt (>20 bubbles) group and a small shunt (>3) bubbles group. They followed the groups prospectively and found 5/16 (31%) of the large shunt group had embolic events despite anticoagulation, whereas none of the small shunt group did (p=.03). These results indicate an association between shunt size and risk of future embolic events.

Venous Gas and DCS

Knowing that PFOs exist, can be clinically detected, and can lead to strokes if clot passes paradoxically through a functional right-to-left shunt, the question is whether of not one can now extrapolate to the decompression situation. As early as 1969, reports existed suggesting that early neurological symptoms after diving could be caused by intracardiac shunts, and specifically by PFOs (Fryer, 1969).

In both diving and altitude, venous gas bubbles may develop when dissolved gas comes out of solution as the ambient pressure decreases during ascent, and the depressurized gas volume expands (and is dissipated). The filtration of bubbles by the lung means they are usually asymptomatic. However, if the lungs are overwhelmed, or if there is a right to left shunt as would exist with PFO (or other atrial-septal defects) then venous bubbles could bypass the lung filter and directly enter the arterial circulation. Considering that the prevalence of PFO in the population is about 25-30%, the incidence of type II DCS is less than might be expected given the known prevalence of PFOs and the documented common occurrence of decompression-induced venous gas bubbles. This may be because bubbles will only pass from the right to the left atria if the normal pressure gradient is reversed.

Pilmanis et al (1996) cite a study supporting the view that some cerebral gas emboli may be tolerable, and may travel back to the venous side without causing obstruction. However, at least 50% of such embolized gas is thought to stay on the arterial side. Although gas emboli behave differently than clots in that they are not rigid and so can conform to vessel shape, their presence remains a key factor in the explanation of neurological decompression sickness.

Spencer (1976) found that venous gas emboli were detectable in 4/11 divers (36%) after a no-decompression (USN tables) 18 m chamber dive for 60 min. He also noted that for the same profile, bubbles were more likely in open water rather than chamber dives. Later, Dunford et al (1988) found venous bubbles in 17% of a sample of sport divers undertaking dives between 6 and 39 msw. Gas bubbles have been found in the venous circulation after ascents from as shallow as 3 m (Eckenhoff et al, 1990).

Eckenhoff et al (1990) studied the dose-response relationship for decompression magnitude and endogenous venous gas bubble formation in humans. Subjects were exposed to pressure of 12, 16, and 20.5 fsw for 48 hrs then returned to surface in less than 5 minutes. There were no DCS cases but a large incidence of venous bubbling. Using a Hill dose-response equation, highly significant fits were obtained and they concluded that 50% of humans generate bubbles after decompression from steady state exposures to 11 fsw, implying that endogenous bubbles form from pre-existing gas collections.

Despite a clear relationship between decompression and development of venous bubbles, some believe the relationship of VGE to DCS is less conclusive (Bayne et al, 1985). This is in contrast to more recent and extensive work by Ron Nishi at DCIEM (1993) who states that although large numbers of bubbles are not necessarily accompanied by DCS, the opposite is usually true i.e. DCS is usually accompanied by bubbles.

Arterial Gas and DCS

In animal studies using pigs, Vik et al (1992, 1993) investigated whether arterial gas was more likely when a PFO was present. Pigs are increasingly being used in research because of their physiological similarity to humans particularly with respect to the cardiovascular system (Broome et al , 1995). In 1992, they compared the rate of paradoxical embolization in PFO to non-PFO pigs at various rates of air infusion, into either the RA or RV (in the PFO group). The incidence of PAE tended to be higher at all infusion rates in the PFO groups compared to controls. In addition, less air needed to be infused in the PFO pigs before arterial bubbles were seen, than in the non-PFO pigs. Finally, the size of the PFO was found to be unrelated to the occurrence of arterial gas.

Then in 1993, the same investigators tested the hypothesis that after rapid decompression pigs with a PFO would be more likely than those without one to have arterialized bubbles. Of 14 pigs, 6 were found to have a PFO and 8 did not. TEE was used to detect arterial bubbles which were found in all 6/6 of the PFO pigs, but only 2/8 in the non-PFO group ($p<.009$). In addition, venous bubble counts in the PFO pigs were lower than in non-PFO pigs. This means that arterial gas bubbles occurred at lower venous bubble loads in PFO pigs, and that pigs with a PFO were more likely to have arterialized gas.

Table 8: Incidence and Time of Detection of Arterial Gas Bubbles in Pigs with PFO and in Pigs Without a PFO
(Table 1 From Vik et al, 1993)

		Arterial Gas Bubbles	
Group	*n*	Incidence	Time, [a] min
PFO	6	6/6 [b] (100%)	<4 [c], 7, 8, 10, 13, 15
Non-PFO	8	1/8 (25%)	10, 12

n Minutes after decompression; [b] $P = 0.009$ compared to the incidence in the non-PFO group; [c] exact time for the occurrence of arterial gas bubbles is not available (*see text*)

In a human population, Glen et al (1995) used transcranial Doppler to determine the incidence of bubbles in the cerebral circulation of divers with and without PFO at various times during safe decompression from air dives. They found 4/17 divers with shunts identifiable by TCD, but none of the divers either with or without PFO had detectable bubbles in the cerebral circulation.

PFO and Diving

Interest in the idea that PFO might be a risk for DCS developed rapidly after 1986 when Wilmshurst et al published a case of Type II DCS in a diver with an ASD, and then hypothesized that this resulted from venous gas passing through the defect.

Subsequently, Moon et al (1989) noted that in1987, 122 cases of Type II DCS occurred in US sports divers, most of whom had conformed to USN Tables, and postulated that PFO could be a risk for DCS (see Table 9). They went on to examine 30 divers with a history of DCS. These were subdivided into those with serious symptoms (18/30) and those with minor symptoms (12/30, 3 of which were *not type II DCS*). Controls were healthy non-diver volunteers from 2 other studies on PFO prevalence.

Table 9: Relation Between Decompression Sickness and Right-to-Left Shunting During Bubble Contrast, Two-Dimensional Echocardiography
(From Moon et al, 1989)

	Decompression Sickness (n = 30)	Controls * (n = 176)
Right-to-left shunt †		
Yes (n = 20)	11	9 ‡
No (n = 186)	19	167

* Controls from refs 4 & 6.
† During breathing at rest
‡ Decompression sickness vs. controls = 25.62, p = 0.0001.

The percentage of divers with R to L shunting was 37%, and of these 11/30 who had shunting, all experienced serious DCS symptoms. The percentage of cases of severe neurological DCS with PFO was therefore 11/18 or 61%. There were no cases of shunting in those with only mild DCS. The authours concluded that PFO represents a risk for the development of DCS. This article by Moon et al led to much discussion.

Also in 1989, Wilmshurst et al (1989, Apr), in a letter to the editor of *The Lancet* reported their belief that cardiac shunts are associated with early neurological symptoms, and usually occur in the context of "safe" dives, but only in dives which have produced venous bubbles (thus not all decompression tables prevent bubble formation). In contrast, these authors proposed that symptoms occurring later after a dive are caused by large tissue nitrogen loads and unsafe decompression procedures.

Eight months later, Wilmshurst et al (1989, Dec) followed up their commentary with an article assessing the relation between shunts and the timing of neurological symptoms after diving (see Table 10). They examined 61 divers with decompression sickness with saline contrast echocardiography, and divided them into 4 subgroups: Ia (n=29) neurological symptoms within 30 min of surfacing, Ib: (n=24) neurological symptoms with onset greater than 30 min after surfacing, Ic: (n=6) joint pain only, and Id (=2) cutaneous symptoms only. The control group was 63 divers with no history of DCS.

The prevalence of shunting was significantly higher in group Ia than in controls or in group Ib. Of those with rapid onset neurological symptoms, 66% were found to have PFOs. The prevalence of PFO in the control group was 24%, similar to that in the general population. Risk factors related to the dive were significantly less prevalent in group Ia than group Ib. Thus, Wilmshurst et al concluded that those with shunts represent a high proportion of cases of early neurologic DCS and they also constitute a majority of cases in which DCS is not explained by the dive profile.

Table 10: Prevalence of Interatrial Shunt in the Groups of Divers
(Table 1 From Wilmshurst et al, 1989, Dec)

	Group Ia	Ib	Ic	Id	Group II
No. of divers	29	24	6	2	63
No. with shunt	19	4	1	1	15
Shunt on Valsalva only	9	0	1	0	7
% with Shunt	66 *	17	17	50	24

* Difference from group II, $p<0.001$; difference from group Ib, $p<0.001$.

One further conclusion, that led to several letters to the editor of *The Lancet* by Smith et al (1990, April, June), was that while the cause of hemiparesis is generally accepted to be cerebral gas embolism, paraparesis may not be caused by autologous bubble formation in the spinal cord as previously believed, but rather by arterial gas bubbles from a shunt or pulmonary barotrauma.

Smith et al (1990 Apr, June) refuted the conclusion that spinal DCS could be due to arterialized gas on the basis of support for the autochthonous hypothesis by animal research and by the fact that Wilmshurst does not explain histologically how intravascular arterial gas could be found in myelin. Smith concludes that a statistical association between PFO and neurological DCS is not proof of the mechanism that causes DCS. Furthermore, Smith et al (1990, Apr, Oct) raised concerns about the methodology used in Wilmshurst's study. The questions of adequate blinding of echocardiographers, selection bias, and variation in methodology from that of Moon's 1989 study were raised. Wilmshurst's responses refuted these claims and notes that Moon's study was, in fact, neither blinded nor controlled.

Cross et al (1990, Sept), report an uncontrolled series of 19 patients referred for DCS who were routinely screened for PFO with contrast echo. They found that in their sample 32% had PFOs, and 50% of neurological DCS cases had shunts. These results were significantly different from Wilmshurst's (1989, Dec) 66% of cases of early neurological DCS with shunts (chi <.05). They concluded that a shunt does not predispose divers to neurological DCS. These results were subsequently severely criticized by Wilmshurst (1990) on the basis of comparison of Cross' pooled group to a selected subgroup of Wilmshurst's (1989 Dec).

In 1992, Cross et al (1992, BMJ) examined PFOs among divers with no history of DCS. They found that 31% of their sample of 78 divers had PFO and concluded that shunts in those without a history of DCS may be irrelevant. Again, Wilmshurst (1992) had an opportunity to be critical of Cross et al, when he pointed out that it is to be expected that a number of divers without DCS would have shunts because of the frequency of shunt occurrence in the general population and presumed lack of effect this would have on diver recruitment. They liken Cross' argument to one stating that a finding of a given number of stroke patients without hypertension indicates that hypertension is not a risk factor for stroke; clearly an illogical statement.

Also in 1992 (Sept), in Switzerland Cross et al present a larger data set in which the prevalence of PFO as determined by contrast TTE in neurological DCS cases (49%) is compared to no-DCS cases (32.7%) and non-divers (39.3%). There were no significant differences among these groups (see Table 11). They also found that the number of dives undertaken by those with multiply treated neurological DCS was higher then in those with only one DCS episode. This finding is not surprising though, because it makes sense that as frequency of diving increases, so does the chance for DCS.

Table 11: Prevalence of Right-to-Left Shunt in Divers and Controls
(Table 1 From Cross et al, 1992)

	Number of Subjects	Number With Shunt	
Neuro DCS	51	25	(49.0%)
No DCS	98	32	(32.7%)
Non-divers	28	11	(39.3%)

DCS = decompression sickness;
Neuro = neurological

Rather than assessing for PFO in divers with known DCS, Wilmshurst et al (1994) assessed DCS among a group of divers with known PFO. The goal was to determine the relation between PFO and any significant arterial desaturation, heart rate and blood pressure responses during physiological maneuvers such as exercise and passive tilt. Their study involved three groups: PFO divers with type II DCS, PFO divers with no DCS, and age and sex-matched control divers. They found no significant differences between these groups on the above-mentioned measures. Because 2 divers in group 1 with the most frequent DCS episodes developed substantial desaturation during exercise they concluded that a large PFO might be associated with clinically relevant desaturation, although this hypothesis was not actually tested.

In an Offshore Technology Report written by Shields et al (1996), the prevalence of PFO in DCS divers (41.4%) was compared with that of non-DCS divers (18.5%) and non-diving controls (22.2%). No significant differences were found among these groups (see Table 12). The authours note however that lack of significant difference may be due to the small number of subjects in the non-diving controls.

Table 12: Distribution of Occurrence of PFO
(Table 25 From Shields et al, 1996)

	Group A	Group B	Group C1	Total
No PFO	17 (58.6%)	22 (81.5%)	7 (77.8%)	46 (70.8%)
PFO	12 (41.4%)	5 *18.5%)	2 (22.2%)	19 (29.2%)

Note: In addition to the 3 subjects that did not take part in this test, in one case the procedure could not be carried out and in an additional 3 cases, the outcome could not be visualized.

More recently, in a well-designed study by Germonpre et al (1998) contrast TEE was used to compare the prevalence of PFO in subjects with neurological DCS to a *matched* population of control divers without DCS (see Table 13). They also examined PFO in relation to spinal and cerebral DCS. The prevalence of PFO in DCS divers was 59.5% compared with 36.1% in matched controls, but this difference did not quite reach significance. However when subgroup analysis was performed, PFO was significantly correlated with cerebral but not spinal DCS. When they examined divers with an unexplained DCS episode, significantly more cerebral (9/12) than spinal DCS cases (4/14) had >20 bubbles passing through the PFO.

Table 13: Prevalence of PFO
(Table 1 From Germonpre et al, 1998)

	Number of Divers With PFO	Number of Divers With Grade 2 PFO
All types of DCS (*n* = 37)	22 (59.5)	19 (51.3)
All control (n = 36)	13 (36.1)	9 (25)
P	0.06	0.03
Cerebral DCS (n = 20)	16 (80)	14 (70)
Matched control (n = 20)	5 (25)	3 (15)
P	0.012	0.002
Spinal DCS (n = 17)	6 35.2)	5 (29.4)
Matched control (n = 16)	8 (50)	6 (37.5)
P	0.49	0.29

The authors conclude that because all known confounding factors have either been matched, or have shown no significant difference between groups, the correlation between PFO and cerebral but not spinal DCS lends support to the hypothesis that "PFO is a cause of DCS with cerebral localization".

Bove (1998) performed a metaanalysis of studies previously published by Wilmshurst et al (1989, Dec), Moon et al (1991), and Cross et al (1992, BMJ). All three of the studies were used to calculate risk for all DCS, but for type II DCS specifically, only data from 2 studies was used (see Table 14). In both the "all DCS" and "type II DCS" analyses, the odds ratio was significantly greater than 1. The presence of PFO increases the risk of DCS in divers with PFO by 1.93 times compared to divers without PFO. For type II DCS the risk is 2.52 times higher in those with PFO.

Table 14: Calculated Probabilities of DCS witth PFO Using Bayes' Theorem[a]
(Table 4 From Bove, 1998)

	All DCS	Type II DCS
P (DCS +/PFO+)	0.00053	0.00047
P (DCS+/PFO-)	0.00028	0.00019
Odds ratio	1.93	22.52
P value	<0.001	<0.001

[a]Odds ratio and P values are derived from logistic regression calculations.

Absolute Risk of DCS in Diving

Cross et al (1994) eventually acknowledge that risk of DCS may be increased by a shunt, but then argue that this increase is small. They note that of approximately 50,000 divers in Britain 15,000 (30%) might be expected to have a PFO. Noting that the number of neurological DCS cases per year is about 100, and that not all shunts will invariably result in DCS, the risk of DCS from a shunt in the total diving population is quite low.

Bove (1998) calculated the combined frequency of type II DCS among military, sport, and commercial divers to be 2.28 per 10,000 dives. An increase of 2.52 times this frequency would lead to an absolute number of 5.7 per 10,000 cases of type II DCS among divers with PFOs. He concludes that despite a 2.5 times greater risk of type II DCS in the presence of PFO, the absolute risk is small enough that there is no basis for recommendations against diving in those with PFO, and that screening is not warranted.

DCS and Altitude

Because altitude decompression is analagous to decompression from saturation, it is thought that more venous bubbling occurs in altitude than with subsaturation decompression in diving, the result being a greater likelihood of paradoxical cross-over. One might therefore expect to find more cerebral symptoms among altitude rather than diving decompressions, and this indeed has been the case (Garrett, 1990).

Although the mechanisms for development of DCS, as well as the proposed pathophysiology for arterialization are similar in diving and flying, much less research on the phenomenon of paradoxical gas embolism has been reported in the altitude literature. Overall, there has been some suspicion that DCS symptoms in altitude situations tend to underreported to a greater extent than they do in diving due the perceived negative career-related consequences.

At the 1991 meeting of the Aerospace Medical Society in Cincinnati, Clarke & Hayes presented their examination of the prevalence of PFO among 24 cases of Type II altitude DCS in naval aviation personnel. They identified 4 cases (16%) of PFO by contrast TTE. They used Moon's 1989 control data to conclude that there was no significant relationship between PFO and type II altitude DCS.

Powell et al (1995) report a single case of a research subject participating in NASA hypobaric decompression testing who was found to have a PFO and was presumed to be at risk for DCS. At ground level, TTE clearly demonstrated left-sided cardiac bubbles. During 3 hours of hypobaric decompression to 21,000 ft the MCA was monitored for the appearance of arterialized bubbles; none were identified, nor were there any DCS symptoms, despite the presence of grade IV precordial bubbles. In this case, the saline contrast bubbles at ground level were clearly arterialized, but the decompression bubbles were not. The authors propose that perhaps the decompression-induced bubbles load was not substantial enough to cause flow reversal. They suggest that the presumption of an increased risk of DCS among those who screen positive for PFO is one to be made with difficulty.

Pilmanis et al (1996) present the first documented right-to-left shunting of venous bubbles after exposure to altitude. Retrospectively examining a database containing 1500 subject-flights to altitudes ranging from 15,000 to 35,0000 feet and exposure times to 8 hours, they identified 6 subjects who demonstrated left ventricular gas emboli. Five subjects became symptomatic at the time of embolization (with joint pain or skin mottling), but no cerebral symptoms were reported. Of the 3 cases investigated with TEE, PFOs were found in 2 cases, and not in 1, despite known embolization. This suggests that more than one mechanism is involved. In light of the fact that in all cases the venous gas score was high at the time of embolization, overload of pulmonary filtration is the second suspected mechanism. Overall the conclusion was that situations which expose subjects to altitudes which result in high venous bubble loads should be avoided.

Webb, Pilmanis, and O'Connor (1998) went on to determine the altitudes at which high venous gas loading occurs. One hundred and twenty four subjects were exposed to simulated altitudes ranging from 11,500 to 25,000 feet for 4 to 8 hours, and were monitored for DCS and for venous bubbling. Venous bubbles were first seen at 15,000 ft and were present in 70% of cases above 22,500 ft. In terms of DCS symptoms, the 5% threshold for symptoms was 20,500 ft with an abrupt increase in symptoms beyond 21,200 ft. These results led the authors to recommend reconsideration of current altitude exposure guidelines.

Screening for PFO

James (1990) cites several studies indicating that nervous system damage can occur without neurological signs. This, in light of the 28 cases of known transient neurological symptoms that have occurred after 41,0000 contrast echo studies, led him to argue against the use of contrast echocardiography in screening divers.

On the contrary, Knauth et al (1997) noted that the prevalence of PFO in the general population was roughly equal to the percentage of divers found to have multiple brain lesions on magnetic resonance imaging (MRI) in a previous study by Reul et al (1995). Knauth et al then postulated that divers with multiple brain lesions may have PFO and that arterialization of bubbles may be the cause. They examined 87 divers without a history of cerebral disease or DCS using TCD and found 25 to have PFO, which they considered to be hemodynamically highly relevant (>20 bubbles) in 13 cases. The prevalence of multiple brain lesions was significantly higher among divers with PFO than those without. Among those with PFOs, the prevalence of multiple brain lesions on MRI was highest among those with hemodynamically relevant PFOs. Considering that none of these divers had a history of DCS the authors suggest that such lesions are a consequence of subclinical cerebral gas embolism. When this work was presented at the American Academy of Neurology annual meeting in 1998, Ries (co-author with Knauth) advocated that the $325 cost of one-time screening is reasonable when compared to the cost of diving equipment (Jeffrey, 1998). Murrison et al (1995) compared the EEGs of divers with type II DCS to non-diver controls and found them to be indistinguishable, which raises the question of the functional significance of the earlier described brain lesions.

Cross et al (1990, Dec) argue that in most cases a contrast study is not performed in isolation of a non-contrast echo study, such that the latter would not be performed if an obvious shunt was detected earlier. They also note that at the time of screening, tissues are not nitrogen loaded, so

arterialized bubbles would not be expected to expand. Finally, they compare the morbidity rate of contrast echo (.07%) to that of a well-accepted screening test, exercise stress testing, which has a complication rate of .09%

The implications of Bove's conclusions are that divers need not be screened prior to initiation of diving, and that those who already know (for some other reason) that they have a PFO can still go ahead and dive. But what about the situation in which DCS has already occurred. Should one then consider evaluation for a shunt?

Wilmshurst (1998, pers comm) recommends three ways to reduce the risk of recurrent DCS in a diver with known PFO;

1. stop diving,
2. modify diving to either stay above 15m depth or, for depths greater than 15m use nitrox or decompress with DCIEM tables, or
3. close the PFO preferably by transcutaneous transvenous methods which do not risk lung injury as open methods would.

In Britain the HSE have required applicants for professional diving with PFO to have transcatheter closure (Wilmshurst, 1998 pers comm). Likewise in the Allied Guide to Diving Medical Disorders published by NATO (1997) states that "significant right-to-left shunts are incompatible with diving unless surgically corrected".

Management of PFO

In the stroke literature, several methods of prevention of recurrent stroke have been used for patients with PFOs, these being antiplatelet medications, anticoagulants, transcatheter closure, and surgery. Mas (1996) argues that closure is the best option in cases of known paradoxical embolism, which are rare and require visualization of thrombus straddling the PFO. In presumed cases however, the best treatment is arguably controversial and requires further risk/benefit analysis to prevent exposure to unnecessary treatment complications.

Nendaz et al (1998) considered risk of recurrence of neurological events, complications, quality-adjusted life years, and death after 5 years in their decision analysis model assessing PFO closure methods. They determined that if the risk of recurrence was .8 to 7% per year, defect closure was the best management strategy. At risk levels of .8% and 1.4% per year, anticoagulation and antithrombotic therapies were better than therapeutic abstention. If however, the risk of recurrence was low (i.e. less than .8% per year) then the best management option was no treatment. They found that the key considerations influencing choice of therapy aside from estimated recurrence risk included bleeding rates, age, and surgery-related case fatality rates.

Several studies have assessed open surgery as a method of closure. Giroud et al (1998) studied 8 stroke patients and found no surgical complications, no recurrence of neurological events, and no residual shunting after PFO closure without post-op anticoagulation. Ruchat et al (1997) also found no post-op complication among 32 patients, although residual shunts were present in 2/32 cases. Homma et al (1997) followed 28 patients with a history of cryptogenic stroke and who underwent surgical PFO closure and found recurrence rate for neurological events of 19.5% overall. This rate was variable when age was considered and proportional hazard regression

analysis revealed an increase in relative risk of recurrence of 2.76 per 10 years of age. They concluded that although surgical closure is easy to perform, it does not guarantee prevention of recurrence.

Non-operative closure of atrial septal defects have been reported since 1976 (Formigari et al, 1998; King et al, 1976). Closure by transcatheter methods remains impossible for some defects especially those greater than 25 mm in size. In addition there are relative contraindications for closure, particularly morphological constraints.

Wilmshurst et al (1996) write about 2 cases of PFO in divers with neurological DCS who were successfully treated with an inverted adjustable button device, one with no residual and the other with a tiny residual shunt. Both divers returned to diving. There is no mention of whether either diver experienced repeated DCS post-procedure. Johnston et al (1996) believe that wider application of invasive shunt closure methods should not occur before the relation between PFO and DCS is further delineated, noting that one must consider the shunt size and not just patency in DCS risk evaluation.

Ende et al (1996) report on their experience with 10 adults who had ASDs or PFOs closed with button devices. Aspirin (5-10mg/kg/day) or Coumadin was administered for 6-12 weeks post-procedure, or until the shunt was completely closed. Closure was complete in 78% of cases at 6 months and 100% of cases by 1 year. There were complications in 3 cases. In one case the device slipped repeatedly across the septum into the left atrium necessitating standard surgical repair. In a second case, the patient experienced palpitations and orthostatic lightheadedness, thought to be due to mechanical irritation and required B-blockade. A third case developed what was presumed to be a left atrial thrombus after 23 months of follow-up and had to be recoumadinized. There were no subsequent neurological events at an average of 32 months follow-up. The later intermediate-term, phase 1 FDA trials for buttoned devices concluded that after 5.5 years of follow-up, 98% of cases had effective ASD closure. Residual shunting remained in 27% of cases after ~60 months. Residual defects were significant enough to require further intervention in 4% of cases.

Justo et al (1996) reviewed the effectiveness of ASD closure in 45 children using the Clamshell double umbrella device. Device placement was optimal in 43 (96%) patients. Closure was complete in only 23+/-14 % of cases by 6 months, and complete in ~64% by 4 years. Complications necessitating the surgical closure of the ASD in two cases were due to device embolization to the right pulmonary artery in one case, and malposition in the septum with significant residual shunting in the second. Other complications included pulmonary edema in one case, and transient loss of femoral pulse (resolved with heparin) in another. The most concerning drawback however, was the prevalence of device arm fracture of 71% (+/- 21%) at 4 years which led to withdrawal of the device from clinical trials. The device has subsequently been redesigned.

The redesigned version (CardioSEAL) was evaluated by Kaulitz et al (1998) in the context of 7 cases of morphologically variant ASDs. The only complication was in one patient who experienced non-sustained SVT; otherwise there were no cases of device embolization, device fractures, thromboembolism, or pericardial effusion. Residual shunting was trivial in 3 cases and mild in 1 case.

Formigari et al (1998) report on the techniques and results of 28 ASD closures (in children) using three different percutaneous devices, these being the Sideris "Buttoned Device", the Das "Angel Wings", and the "Amplatzer". For all groups, fluoroscopy times were similar, but procedure time was shortest for the Amplatzer and longest for the buttoned device. Definitive closure occurred in all cases except 1 buttoned device. Follow-up times were longest for buttoned devices at 40+/- 2 months, compared with 27+/- 2 mo. for the Angel Wings, and 5+/3 mo for the Amplatzer. In terms of complications, there were 2 cases of transient myocardial ischemia secondary to coronary air embolism in the buttoned devices, and 1 case of pericardial tamponade with the Angel Wings. Others have reported failures with this device also requiring emergency surgical intervention (Agarwal et al, 1996). There had been no complications with the Amplatzer device. Cost, according to these authours was least expensive for the buttoned devices. Overall they concluded that the Amplatzer device is preferable.

Wilmshurst has subsequently stated (1998, pers comm) that PFOs in most individuals are approximately 1-2 mm in size compared to PFOs of 10 mm or greater among those who get DCS. He has moved from a buttoned device to using the Amplatz septal occluder, which he considers to be the best device currently available. He prescribes low dose ASA for 6 months post-procedure until endothelialization occurs.

The most recent results of the World Study on closure with the Amplatzer indicate that a total of 936 ASDs have been closed as well as 86 PFOs. Closure rates for PFOs are good, with 100% being closed at 24 hours, compared with 100% at 1 year for the ASD cases (98.9% at 1 month). There were 24 complications among ~1000 patients, the majority of which included device embolization (9/24), TIA/embolization (4/24), and arrhythmia (3/24).

Limitations

There are several factors that limit the generalizability and hence the conclusions that can be drawn from the studies performed to date. These include variation in study groups used (i.e. sport, commercial, or military divers), variation in control groups used (ie. matched vs. unmatched, diver vs. non-diver), differing techniques for PFO detection (ie. TTE vs. TEE), and variability in definition of DCS or severity of cases selected to be members of the study group.

CONCLUSIONS

Nonetheless, several conclusions can be tentatively drawn on the basis of available research:

1. For detection of PFO, TCD is probably adequate, but contrast TEE is the gold standard and remains more commonly used.

2. There seems to be a relationship between crypogenic stroke and the presence of PFO, as well as the size of the PFO.

3. Animal studies show increased arterial bubbles at lower venous bubble loads in pigs with PFO than in those without.

4. The weight of evidence favours an association between diving DCS and PFO. This association remains less clear in the case of altitude DCS, with fewer studies available on this topic. PFO increases the relative risk for type II DCS but the absolute risk remains low.

5. With altitude, high bubbles loads may favour pulmonary overload as a mechanism for embolization.

6. The issues of screening remains controversial, although the absolute increase in risk of DCS as a result of PFO seems small.

7. Should closure be chosen for management, the transvenous Amplatzer appears to be the best available option at this time.

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Additional info and quotes, not included but possibly relevant.

* Risk of venous bubbling seems to be reduced in aerobically trained runners compared to sedentary subjects in some studies, but others have shown no relation to fitness and DCS (Broome et al, 1995).

* Knowing the incidence of PFO in the general population, one can assume that the incidence of PFO in divers would be similar since there is no selection bias in a person's choice to take up diving based on the presence of an "unknown" PFO.

* Is there any info on whether known PFO cases choose NOT to dive more frequently than unknown cases later discovered?

* PFO rates in divers and controls, not in stroke patients
Moon (1989) 37% diver
Cross (1990) 31.6% diver
Wilmshurst (1989b) 25/61 diver, 24% control
Germonpre (1998) 36.1 % control
Lynch (1984) in Glen et al (1995) TTE 5-20%
From Kerut: Zhu et al (1991) – 38%
From Kerut : Job et al (1994) – 43%

* Difference in contrast media:
Jauss (1994): Galactose particle suspension is stable for about 60 sec after intravenous injection, which may lead to higher sensitivity in PFO detection than with other contrast media such as air or gelatine. This however necessitates determining a time limit to prevent false positives due to lung passage.
Definition of presence of PFO based on number of bubbles passed per cardiac cycle etc.

* From an epidemiological perspective, the characteristics of a useful population based screening measure are: (From Chan Shah's book on Public Health)

1) Conditions for which screening is used should be important health problems i.e. The incidence should be sufficiently high that the cost of screening is not prohibitive.
2) Facilities for diagnosis and treatment should be available
3) Effective, non-controversial treatment for patients with confirmed condition should be available
4) Tests should have high sensitivity and specificity; screening must be safe, rapidly applied, and acceptable to the population being screened
5) The natural history of the condition should be understood, such that if detection and treatment do not alter the natural history, screening should not be implemented
6) Policy must stipulate what action will be taken in borderline cases to avoid overdiagnosis
7) Maximum benefit for minimum cost must be achieved by comparing the costs and efficiency of various screening methods

8) Control and screened groups should be compared at regular intervals to determine whether the screening procedure and subsequent investigations have an effect on the control group that is greater than just regular observation (placebo effect)
9) Compliance with screening recommendations
10) Screening programs should be a continuous process

Table 4. FLOW-PATENT FORAMEN OVALE AND ECHOCARDIOGRAPHY

Study	Number of Patients	Modality	In Vivo Resting Conditions (%)	Augmentation Maneuvers (%)
Chen et al[48]	32	TTE	25	38
		TEE	44	63
Konstadt et al[155]	50	TEE	10	22
Porembka et al[245]	30	TEE	27	—
Stollberger et al[300]	264*	TEE	15	—
Lechat et al[169]	100	TTE	5	10
	60		18	24
Hausmann et al[113]	198	TTE	8	—
		TEE	22	—
Jaffe et al[131]	30	TEE	10	Unchanged
Guggiari et al[104]	189	TTE	8	10
Black et al[29]	101	TTE	6	Unchanged
	51	TEE	8	—
Siostrzonek et al[280]	150	TTE	5	6
	160	TEE	12	20

*Suspected embolic events.

From Porembka, 1996

Table 1: Frequency of DCS in Sport, Military, and Commercial Air Diving Populations

Source Reference	Military (13)	Sport (11,12)	Commercial (14)	All
Total dives[a]	648,488	2,577,680	43,063	3.269,231
Total DCS[a]	172	878	152	1,202
Type II DCS[a]	86	649	9	744
Incidents DCS[b]	2.65	3.41	35.3	3.68
Incidents DCS II	1.33	2.52	2.09	2.28

[a]Values are number of events; [b]incidents per 10,000 dives, DCS II - DCS type II.

From Bove, 1998

Accuracy of Different Echocardiographic Criteria for Identifying an Autopsy-Proven Patent Foramen Ovale

Definition	Sensitivity (%)	Specificity (%)	Pos Predictive Value (%)	Neg Predictive Value (%)	Prevalence PFO (%)
Contrast TEE					
Bubbles LA/heart cycles					
>1/3	89	100	100	96	23
>2/3	67	100	100	90	17
>5/3	55	100	100	87	14
>2/immediately	44	100	100	84	11
Multiple/ 1–2	33	100	100	81	9
Color Doppler TEE					
Shunt direction					
Right-to-left and/or left-to-right	100	100	100	100	26
Right-to-left, not left-to-right	89	100	100	96	23

From Schneider et al, 1996

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EXECUTIVE SUMMARY

A patent foramen ovale (PFO) is a small opening between the right and left cardiac atria, a persisting remnant of a physiologic communication present in the fetal heart. This normally closes after birth, but remains patent through to adulthood in up to a third of normal adults. A patent PFO is a potential conduit for blood clot (resulting in a stroke), or venous gas bubbles during decompression, (resulting in type II neurologic decompression sickness). There has been considerable controversy about the significance of a PFO as a possible mechanism for type II decompression sickness. Despite the high prevalence of PFO in the general population, and the relatively common occurrence of venous gas bubbles in diving and altitude exposures, the incidence of type II DCS in diving or with altitude exposure is low.

. This paper reviews the literature with respect to the potential for right-to-left embolization through a PFO, relation of PFO to DCS, screening techniques for PFO, and treatment options. The literature supports a relationship between the presence and size of PFO and cryptogenic stroke (stroke, generally in younger individuals with no other identifiable risk factors). The weight of evidence also favours an increased relative risk of type II DCS with a PFO, although the absolute increase in risk accrued is small. The gold standard for PFO screening is a trans-esophageal echocardiographic (TEE) and colour flow study, but trans-cranial Doppler (TCD) with contrast is a promising technique with good accuracy compared with TEE.

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Decompression Sickness, Altitude, Diving, Foramen Ovale